

REMARKS

Claims 1-23 are pending in the present application. Claims 1-12 are rejected under 35 USC §112. Claims 1, 6, 9, 11-12 and 13-23 are rejected under 35 USC §103(a). Claims 13-23 are rejected under the judicially created doctrine of obviousness-type double patenting. Applicants respectfully request reconsideration of the application, withdrawal of all rejections, and allowance of the application in view of the amendments and remarks below.

The Invention

The present invention provides novel condensation drug aerosols and methods for producing such aerosols. These condensations aerosols have little or no pyrolysis degradation products. The unique method for generating or producing such aerosols employs rapid vaporization of the drug to minimize drug degradation during the process. These vaporized drugs are subsequently condensed to form particles of a desirable particle size for inhalation. These aerosols are especially useful in the treatment of acute or chronic conditions wherein rapid onset of treatment is desirable.

The Amendments to the Claims

Without prejudice to the Applicants' rights to present claims of equal scope in a timely filed continuing application, to expedite prosecution and issuance of the application, the Applicants have amended Claims 1-3, 5, 7, 8, 13, 15 and 17-23 and cancelled Claims 4, 9-12, 14 and 16. The Applicants also have presented new Claims 24-44. The amended claims and the new claims are supported by the specification (see below for examples of such support).

| Claim | Examples of Support in the Specification |
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| Claim 1 | Paragraphs 0005, 0017, 0020, 0022; Example 2 |
| Claim 2 | Paragraph 0022 |
| Claim 3 | Paragraph 0031 |
| Claim 5 | Paragraph 0028 |
| Claim 7 | Paragraph 0029 |
| Claim 8 | Paragraph 0030 |
| Claim 13 | Paragraphs 0005, 0017, 0020, 0022; Example 2 |
| Claim 15 | Paragraphs 0005, 0017, 0020, 0022, 0032, 0033; Example 2 |
| Claim 17 | Paragraphs 0005, 0017, 0020, 0022, 0032, 0033, 0064, 0065; Example 2; Figure 1 |
| Claim 18 | Paragraphs 0063 |
| Claim 19 | Paragraphs 0063 |
| Claim 20 | Paragraphs 0063 |
| Claim 21 | Paragraphs 0060; Example 2 |

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| Claim 22 | Paragraphs 0031 |
| Claim 23 | Paragraphs 0064, 0065 |
| Claim 24 | Paragraphs 0001 [incorporates by reference U.S. provisional application Ser. No. 60/317,479 (see, e.g., page 30, lines 25-27)], 0022 |
| Claim 25 | Paragraphs 0001 [incorporates by reference U.S. provisional application Ser. No. 60/317,479 (see, e.g., page 30, lines 25-27)], 0022 |
| Claim 26 | Paragraph 0018 |
| Claim 27 | Paragraph 0018 |
| Claim 28 | Paragraph 0017 |
| Claim 29 | Paragraph 0017 |
| Claim 30 | Paragraph 0029 |
| Claim 31 | Paragraph 0030 |
| Claim 32 | Paragraph 0022 |
| Claim 33 | Paragraphs 0001 [incorporates by reference U.S. provisional application Ser. No. 60/317,479 (see, e.g., page 30, lines 25-27)], 0022 |
| Claim 34 | Paragraphs 0001 [incorporates by reference U.S. provisional application Ser. No. 60/317,479 (see, e.g., page 30, lines 25-27)], 0022 |
| Claim 35 | Paragraph 0018 |
| Claim 36 | Paragraph 0018 |
| Claim 37 | Paragraph 0032 |
| Claim 38 | Paragraph 0032 |
| Claim 39 | Paragraph 0029 |
| Claim 40 | Paragraph 0030 |
| Claim 41 | Paragraph 0059 |
| Claim 42 | Paragraph 0059 |
| Claim 43 | Paragraph 0062 |
| Claim 44 | Paragraph 0060 |

The amendments to the claims do not introduce new matter. Applicants respectfully submit that the amendments to the claims put the case in condition for allowance. The Examiner is respectfully requested to enter the amendments to the claims and allow all amended claims.

The Rejection under 35 U.S.C. §112

The Examiner rejected Claims 1-12 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the phrase “by the patient of the formation of, and delivery of, the condensation aerosol” in Claims 1 and 9 was found to be unclear and redundant. Claim 1 has been amended to eliminate this phrase. Claim 9 has been cancelled.

The Rejection under 35 U.S.C. §103(a)

The Examiner rejected Claims 1, 6, 9, 11-12 and 13-23 under 35 U.S.C. §103(a) as being unpatentable over Bartus et al. (6,514,482) in view of Staniforth et al. (20010020147 A1) and further in

view of Faithfull et al. (6,041,777). In support of this rejection, the Office Action states that “Bartus teaches a method of pulmonary delivery of a medicament, which includes administering . . . particles . . . , where the particles preferably have an aerodynamic diameter between about 1 and 5 μm .” Office Action at 3. The Office Action further states that Bartus discloses medicaments containing from 1 to about 90 weight percent of drugs, including stimulants and appetite suppressants, etc., that are delivered via a dry powder inhaler, metered dose inhaler, nebulizer or instillation techniques. *Id.*

The Office Action states that Bartus lacks “specific disclosure on ephedrine or fenfluramine” but that “Staniforth teaches delivery of a drug comprising a multiple unit dosing device, wherein the particles comprise at least about 80% drug and preferably at least 90%.” Office Action at 3. According to the Office Action, suitable drugs for the formulation include ephedrine, and these formulations can be delivered to the lungs via inhalation. *Id.* at 4.

The Office Action states that Bartus and Staniforth lack “teachings on producing condensation aerosol and also lack specific disclosure on the presence of less than 5% degradation products.” *Id.* at 4. The Office Action states in summary that Faithfull teaches methods and apparatus for closed-circuit ventilation therapy, including the use of nebulizers to provide fluorochemicals and/or pharmaceutical agents, heated above body temperature, to a ventilating gas in the form of a vapor and that this is accomplished by spraying or contacting a wetted surface or wick with the gas to form droplets. *Id.* at 4.

The Office Action states that it “would have been obvious to a person of ordinary skill in the art at the time the invention was made to have modified the method of delivering a medicament to a patient’s respiratory tract of Bartus, by adding the specific stimulants of Staniforth and the steps of heating the composition and having patient inhale the condensates, because of the disclosed benefits of such a method, including minimized trauma to the lungs and a better resolution of pulmonary and systemic disorders, as taught by Faithfull.” *Id.* at 4-5.

Applicants respectfully disagree in view of the elements of the pending claims and the disclosures of Bartus, Staniforth and Faithfull. Bartus fails to teach or disclose a condensation aerosol. Rather Bartus is directed to a method of delivering low tap density particles for the treatment of CNS disorders and in particular, Parkinson’s disease, via dry power inhalers or metered dose inhalers. Nowhere does Bartus disclose or suggest an aerosol particle formed as a condensate of a vaporized drug, nor the advantages obtained by such a condensate aerosol. Additionally, Bartus lacks teachings on heating the composition. Dry powder inhalers, metered dose inhalers, nebulizers or instillation techniques do not vaporize the drug and then form a condensate of the drug. Additionally, in Bartus there is no disclosure of how one would form such particles of an antiparkinsonian drug or any other drug compound to generate an aerosol characterized by less than 10% drug degradation products, or how to obtain aerosols having an MMAD of less than 5 microns when vaporizing the drug. Nor does Bartus disclose heating a thin layer, containing

the drug, on a solid support. These elements, which are not taught in Bartus, are required by independent Claims 1, 13 and 15.

Staniforth also fails to teach or disclose a condensation aerosol. Rather, Staniforth is directed to a delivery device and method for the oral administration of therapeutic agents in powder form for delivery to the gastrointestinal tract. The device and methods taught in Staniforth are specifically designed to avoid drug delivery to the lungs. Staniforth teaches particles having a mean diameter of greater than 10 microns to about 1 mm so that “an effective dose of the drug **cannot** be delivered into the lower lung” of a patient. Staniforth at paragraph [0029] (emphases added). Additionally, Staniforth, explicitly states that the multiparticles of its formation are “**not** dispersed in a cloud or mist, which effectively minimizes inhalation of the active agent into the lungs of the patient.” *Id.* at paragraph [0040] (emphasis added). Nowhere does Staniforth disclose or suggest an aerosol particle formed as a condensate of a vaporized drug, nor the advantages obtained by such a condensate aerosol. Staniforth, like Bartus, fails to disclose generating an aerosol characterized by less than 10% drug degradation products from the vaporization process, and formation of an aerosol having an MMAD of less than 5. The Examiner has cited Staniforth as supporting the desirability of using particle inhalation delivery techniques for the administration of therapeutic agents such as ephedrine. However, Staniforth actually teaches the opposite by specifically describing devices, particle sizes and methods that will prevent drug delivery into the lungs. Thus, the combination of Staniforth with Bartus is illogical and even if such combination were to be made, would in no way teach the present invention.

Faithfull does not cure these deficiencies or make obvious in view of Bartus and/or Staniforth how to accomplish these tasks. Faithfull does not disclose or teach a condensation particle or aerosol as defined by the Applicants’ claims or how to make such an aerosol. Faithfull discloses the use of a warmed fluorochemical as a solvent for delivering the active compound “oxygen” to the lungs of the patient using a ventilation system. The active or therapeutic compound or drug in Faithfull is not vaporized and subsequently condensed into aerosol particles, as is set forth in Claims 1, 13 and 15 of the present application. Moreover, there is no teaching in Faithfull of drawing air through an enclosure being effective to condense a vapor to form a condensation aerosol, as required in Claim 17. Rather, Faithfull teaches away from such a condensation aerosol, as oxygen gas is already being passed through the system described by Faithfull and no condensation aerosol is formed. Instead, Faithfull requires the use of a wetted surface or wick to get the fluorochemical (solvent) to form a droplet. Moreover, as is stated in the Office Action, the fluorochemical in the Faithfull reference, unlike the present invention, is being delivered to the lung as a vapor and not an aerosol. See Office Action at 4 (“As the fluorochemical **vapor** cools in the body it is deposited on the pulmonary surfaces” (emphasis added)). Faithfull does not disclose how to make a condensation aerosol having the purity disclosed in the present application, or

how to obtain MMAD sizes of less than 5 microns for condensation aerosols. Nor does Faithfull disclose heating a thin layer, containing the drug, on a solid support.

According to the MPEP § 2143, "to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art references (or references when combined) must teach or suggest all the claim limitations." Obviousness cannot be established by combining teachings in the prior art, absent some teaching or suggestion in the prior art that the combination be made (*In re Stencel* 828 F. 2d 751, 4 USPQ2d 1071 (Fed. Cir. 1987); *In re Newell* 891 F. 2d 899, 13 USPQ2d 1248 (Fed. Cir. 1989)).

As noted above, neither Bartus nor Staniforth is directed to volatilizing drugs or to forming condensation aerosols suitable for inhalation characterized by less than 10% drug degradation products and an MMAD of less than 5 microns. Moreover, as Staniforth is directed to avoiding delivery to the deep lung, there would be no motivation to combine it with Bartus. Faithfull does not cure the deficiencies of Bartus and/or Staniforth. Accordingly, the Office Action fails to establish even a *prima facie* case of obviousness as each and every element of the invention is not taught or disclosed by these references. Moreover, there would be no motivation to combine the references to achieve the presently claimed invention. Even if the cited references were combined, the claimed invention would not result because neither Bartus, Staniforth nor Faithfull is directed to heating a thin layer containing a drug, on a solid support, or to forming condensation aerosols suitable for inhalation that are characterized by less than 10% drug degradation products and an MMAD of less than 5 microns.

The Office Action suggests that condensates by their nature have a high percentage of purity of the drug and less degradation products. Applicants respectfully disagree. The mere fact that an aerosol is formed by condensation does not mean that the aerosol will have a high percentage of drug and less degradation products.

Claims 2, 3, 5-8 and 24-29 which depend from Claim 1 patentably define over Bartus, Staniforth and Faithfull for the same reasons as Claim 1. Claims 30 and 31 which depend from Claim 13 patentably define over Bartus, Staniforth and Faithfull for the same reasons as Claim 13. Claims 17-23 and 32-44 which depend from Claim 15 patentably define over Bartus, Staniforth and Faithfull for the same reasons as Claim 15.

Finally, the Examiner rejected Claims 1, 6, 9, 11-12 and 13-23 under 35 U.S.C. 103(a) as being unpatentable over Bartus et al. (6,514,482) in view of Staniforth et al. (20010020147 A1) and further in view of Byron et al. (20040016427 A1). Office Action at 5. The Office Action states that Bartus and Staniforth "lack disclosure on condensation aerosols and the devices for producing condensates involved in the method

of therapy,” but that “Byron et al. disclose a method and apparatus for generating an aerosol . . . formed by supplying a material in liquid form to a tube and heating the tube such that the material volatizes and expands out of an open end of the tube.” *Id.* The Office Action goes on to state that the volatized material combines with ambient air such that volatized material condenses to form the aerosol and that the aerosols are intended for inhalation and typically have a mass median particle diameter of less than 2 microns. Thus according to the Office Action, it would have been obvious to take the device of Byron and use it to deliver the aerosolized composition of Bartus and the specific stimulants of Staniforth to a subject’s respiratory tract as it would be desirable to provide an aerosol delivery article capable of making small particles without exposure to significant heat or high temperatures. *Id.* at 6.

Applicants respectfully disagree. As noted above, the combination of Bartus and Staniforth is illogical and neither Bartus nor Staniforth is directed to volatizing drugs or to forming condensation aerosols suitable for inhalation characterized by less than 10% drug degradation products and an MMAD of less than 5 microns.

One of skill in the art seeking to prepare and administer aerosolized compositions for delivery to a subject’s respiratory tract without exposure to significant heating or high temperatures would not have to look beyond the disclosure of Bartus. Moreover, Bartus does not teach that small particles are desirable. To the contrary, Bartus states that larger, low density particles aerosolize more efficiently and avoid phagocytic engulfment by alveolar macrophages more effectively than smaller, denser aerosol particles. Bartus col. 13, lines 61-64.

“The aerodynamic diameter can be calculated to provide for maximum deposition within the lungs. Previously this was achieved by the use of very small particles of less than about five microns in diameter, preferably between about one to about three microns, which are then subject to phagocytosis. Selection of particles which have a larger diameter, but which are sufficiently light (hence the characterization “aerodynamically light”), results in an equivalent delivery to the lungs, but the larger size particles are not phagocytosed. Improved delivery can be obtained by using particles with a rough or uneven surface relative to those with a smooth surface” (Bartus col. 13, line 65 to col. 14, line 7).

As pointed out in the Office Action, the aerosols generated by the device of Byron et al. typically have a mass median particle diameter of less than 2 microns, while Bartus teaches that the preferred size range of particles is at least about 5 microns, preferably between about 5 microns and 30 microns. See, e.g., Bartus at col. 12, lines 60-66; col. 14, lines 12-14. Thus, Bartus teaches away from delivering its compositions using the device of Byron et al.

Moreover, one of skill in the art would not have a reasonable expectation that the device of Byron et al. would successfully form condensation aerosols suitable for inhalation that are characterized by less

than 10% drug degradation products and an MMAD of less than 5 microns from the compositions of Bartus and/or Staniforth. For instance, under the method of Byron et al., the compositions of Bartus (“solid component”) would have to be put into liquid form by combining with a “liquid component.” Byron et al., paragraph 0076. However, Byron et al. fails to provide specific guidelines for selecting an appropriate “liquid component” for a given drug (“solid component”) or for predicting what effect heating the mixture will have on the solid component. This is further complicated when the solid component contains one or more additional component in addition to the drug, such as the surfactants, phospholipids, amino acids, etc., taught in Bartus. Bartus, col. 8, lines 42 to col. 11, line 53.

Finally, these references do not teach or suggest all of the elements of independent Claims 1, 13 and 15. Like Bartus and Staniforth, Byron et al. lacks specific disclosure on the presence of less than 10% degradation products. Furthermore, neither Bartus, Staniforth nor Byron et al. describes heating a thin layer, containing the drug, on a solid support.

Thus, these references singly or in combination do not teach or suggest all the claim elements, but rather teach away from the claimed invention. Accordingly, the Office Action fails to establish even a *prima facie* case of obviousness. Moreover for the same reason, there would be no motivation to combine the references to achieve the presently claimed invention, nor is it seen how the combination of the references would achieve the presently claimed invention.

Claims 2, 3, 5-8 and 24-29 which depend from Claim 1 are not obvious for the same reasons as Claim 1. Claims 30 and 31 which depend from Claim 13 are not obvious for the same reasons as Claim 13. Claims 17-23 and 32-44 which depend from Claim 15 are not obvious for the same reasons as Claim 15.

Accordingly, and in light of the foregoing arguments, the Applicants respectfully submit that these amendments put the case in condition for allowance and request that the Examiner reconsider and withdraw all rejections based on 35 U.S.C §103.

Double Patenting

Claims 13-23 were rejected under the judicially created doctrine of obviousness-type double patent as being unpatentable over claims of U.S. Patent No. 6,780,399 B2, as these claims are “either anticipated by, or would have been obvious over, the reference claims.” Office Action at 6-7. Also, Claims 13-23 were provisionally rejected under the doctrine of obviousness-type double patenting as being unpatentable over claims of copending Application No. 10/815,527 and claims of copending Application No. 10/150,268. *Id.*

Applicants have filed with this response Terminal Disclaimers with regard to U.S. Patent No. 6,780,399 B2 and copending Application Nos. 10/815,527 and 10/150,268. Applicants believe that this

addresses the Examiner's concerns and respectfully request reconsideration of the application, withdrawal of all rejections, and allowance of the application in view of these actions and remarks.

Conclusion

The Applicants appreciate the Examiner's careful and thorough review of the application and submit that the Examiner's concerns have been addressed by the amendments and remarks above. The Applicants accordingly request the Examiner to withdraw all rejections and allow the application. In the event the Examiner believes a telephonic discussion would expedite allowance or help to resolve outstanding issues, prosecution of the application, then the Examiner is invited to call the undersigned.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefore to deposit account No. 19-5117, if not otherwise specifically requested. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to be charged to deposit account No. 19-5117.

Respectfully submitted,

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